PATENT COOPERATION TREATY

Written R20

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.11.2005
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PC25634A	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003310	11.10.2004	23.10.2003

Applicant
PFIZER PRODUCTS INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25634A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003310	International filing date *(day/month/year)* 11.10.2004	Priority date *(day/month/year)* 23.10.2003
International Patent Classification (IPC) or national classification and IPC C12N1/20		
Applicant PFIZER PRODUCTS INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.11.2004	08.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Perez, C Telephone No. +49 89 2399-2484

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003310

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-27 as originally filed

Sequence listings part of the description, Pages

1-8 as originally filed

Claims, Numbers

1-35 as originally filed

Drawings, Sheets

1/4-4/4 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18 as far as IA is concerned

because:

☒ the said international application, or the said claims Nos. 18 as far as IA is concerned relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 6-8, 10, 30-35
	No:	Claims	1-3, 5, 9, 11-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-35
Industrial applicability (IA)	Yes:	Claims	1-17, 19-35
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

1. Additional remark to item III (no opinion)

Claim 18 is directed to an in vivo therapeutic method, which is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of said claims (Article 34(4)(a)(i) PCT).

2. Additional remarks to item V (reasoned statement under Rule 66.2(a) (ii) with regard to novelty, inventive step or industrial applicability)

2.1 Present application

The present application is directed to isolated pigmented anaerobic bacterial isolates identified by their 16S rRNA DNA that cause periodontal diseases in companion animals. Said isolates are characterized by comprising a 16S rRNA DNA sequence having at least 95 % or 99 % or 99.5 % homology with a sequence selected from SEQ ID N° 3, 4, 5, 6, 9, 10 and 13. In particular three bacterial isolates, a Bacteroides denticanoris corresponding to ATCC PTA-5881, a Porphyromonas levii corresponding to ATCC PTA-5882 and a Tannerella forsythensis corresponding to ATCC PTA-6063 are disclosed. Said isolates are used as immunogenic composition or vaccine for the treatment or prevention of peridontal diseases. Probes consisting of 15 contiguous nucleotides of any of the above sequences are also used as part of a kit for the detection of Bacteroides, Porphyromonas or Tannerella species.

2.2 Prior art documents

The present communication refers to the documents cited in the International Search Report (ISR). Said documents are numbered as in the ISR, i.e. D1 corresponds to the first document cited in the ISR. The numbering will be adhered to in the rest of the procedure.

These prior art documents disclose, among other, the following data:

(i) **D1** discloses a genomic DNA corresponding to the partial sequence of the 16S rRNA gene of a Bacteroides strain, strain 0103 800. Said sequence exhibits high percent identity with all 16S rRNA DNA sequences of the application derived from Bacteroides denticanoris strains:

- it shares 98.7 %, 98.12 %, 98.6 %, 98.6 % and 98.93 % identity with the entire SEQ ID N°3, 6, 9, 10 and 13 of the present application respectively;

- it exhibits 100 % identity with fragments of said sequences, for example [332-550] of SEQ ID N°3, [145-424] of SEQ ID N°6, [332-565] of SEQ ID N°9, [191-313] of SEQ ID N°10, and [68-179] of SEQ ID N°13.

(ii) **D2** discloses a genomic DNA corresponding to the sequence of the 16S rRNA gene of a Tannerella forsythensis strain TR6. Said sequence exhibits 99.04% identity with the entire SEQ ID N°5 of the present application. Moreover it is 100 % identical with fragment [311-520] of said SEQ ID N°5. Furthermore Bacteroides forsythus is provided as a synonym of Tannerella forsythensis.

(iii) **D3** corresponds to an earlier application from the present Applicant already disclosing bacterial isolates identified by their 16S rRNA DNA that cause periodontal disease in companion animals, in particular bacteria from the genus Porphyromonas. Many of the 16S rRNA DNA sequences share high percent identity with the sequences of the present application. As an example, the sequence SEQ ID N°89 (ADH52847) corresponding to a 16S rRNA DNA sequence of a Porphyromonas gulae strain B69, shares 100 % identity with fragments [69-180] of SEQ ID N°3, [831-942] of SEQ ID N°6, [235-309] of SEQ ID N°4, [32-176] of SEQ ID N°5, [234-302] of SEQ ID N°9, [68-179] of SEQ ID N°10 and [331-565] of SEQ ID N°13. Also disclosed are vaccine composition and kit comprising live or inactivated isolated bacteria, useful for treating or preventing periodontal diseases, as well as hybridization kit for the detection of Porphyromonas species (p.48, l.30 - p.53, l.24).

(iv) **D4** discloses the identification of 275 species or novel phylotypes in human diseased patients, among which many species from the Bacteroidetes genus such as Bacteroides forsythus and various Porphyromonas species. Moreover is refers on page 3780, right column, second paragraph, to a commonly accepted rule for the definition of a bacterial species: a 2 % difference in the 16S RNA DNA sequences is generally used as an indication that the corresponding bacteria belong to different species.

(v) **D5** reports the treatment of periodontal diseases by administration of metal ions to the site where the microorganisms reside. These ions are microbicidal to the bacterial pathogens such as B. forsythus or P. gingival is as shown in example 4, on dogs (see

Table 1).

2.3 Statement with regard to novelty and inventive step (Articles 33 (2) and (3) PCT)

2.31 Novelty

The subject-matter of **claims 1-3, 5, 9, 11-29** does not meet the requirements of Articles 33 (2) and (3) PCT, because said claims lack novelty in view of D1 and/or D2 and/or D3 and their lack of clarity.

i) Given the wording of the specification, in particular on page 3, lines 1-23, the subject-matter of claim 1 is interpreted as an isolated pigmented anaerobic bacterium "suitable for causing periodontal disease in companion animals" (PCT Guidelines, 11.03.2004, Chapter 5.21-5.23), which is only characterized by the at least 95 % homology of its 16S rRNA DNA sequence to the sequences referred to in claim 1. In other words any isolated pigmented anaerobic bacterium whose 16S rRNA DNA sequence fulfills the conditions set in claim 1, is considered to inherently cause periodontal diseases in companion animals. In this context D1 and D2 disclose 16S RNA sequences of Bacteroides and Tannerella strains which are 98 to 99 % identical to at least one of the whole sequences referred to in claim 1 of D1 and D2 respectively (see § 2.2 i and ii). Such high percentage of identity at the 16S RNA DNA level, less than 2 % difference, is generally recognised as meaning that the 2 corresponding bacteria belong to the same species (see § 2.2 iv). Thus D1 and D2 are prejudicial to novelty of claims 1, 2 and/or 9, because the disclosure, in D1 and D2 respectively, of the 16S rRNA DNA of the Bacteroides species 0103 800 and the Tannerella forsythensis TR6 strain, renders the isolation of said bacterial strains implicit (see PCT Guidelines, 11.03.2004, Chapter 12.04) and the fact that said bacteria are pigmented, anaerobic and suitable for causing periodontal diseases are inherent features of these bacterial species. This lack of novelty also applies to claims 5 and 11 because "Bacteroides denticanoris" is only an arbitrary denomination, and the feature introduced in claim 11 does not restrict the scope of claim 1.Thus D1 and/or D2 anticipate novelty of **claims 1-2, 5, 9 and 11**.

ii) Moreover it is pointed out that claims 1-3 refer to "a" sequence and not "the whole"

sequence selected from SEQ ID N°3, 4, 5, 6, 9, 10 and 13. Since the 16S rRNA DNA sequences provided by D1, D2 and the SEQ ID N°89 of D3 all exhibit 100 % identity to fragments of SEQ ID N°3, 4, 5, 6, 9, 10 and 13 (see § 2.2 i - iii), the bacteria referred to in said documents are prejudicial to novelty of **claims 1-3 and 5, and 11** (see the detailed reasoning above). With regard to D3, this novelty objection further applies to **claims 12-29**, because said document also provides vaccine composition for treating and preventing periodontal diseases as well as hybridization kits for the detection of Porphyromonas species (see § 2.2 iii).

2.32 Inventiveness

The subject-matter of **claims 1-35** does not meet the requirements of Article 33 (3) PCT, because said claims do not involve an inventive step in view of the teachings of D3 in combination with D4 and D5.

D3 is the closest prior art because it already describes vaccines for treating or preventing periodontal diseases in companion animals. The present application differs from D3 by the nature of the bacterial isolates comprised in said vaccine preparation.

Thus the problem to be solved is to provide alternative vaccine for the treatment and prevention of periodontal diseases in companion animals.

However it is clear from the overall literature on periodontal diseases that there are hundreds of bacterial species which are involved in said diseases. For example, D4 reports that 275 species or novel phylotypes were identified in human diseased patients, among which many species from the Bacteroidetes genus such as Bacteroides forsythus and various Porphyromonas species (see § 2.2 iv). Thus the disclosure of D4 shows that new bacterial isolates involved in periodontal diseases are frequently being identified and that novel bacterial isolates can be expected to be identified in the future. Moreover the results on dogs of D5 confirm that many of these bacterial species are also pathogens for companion animals, for example, Bacteroides forsythus (see § 2.2 v).

In this context the skilled person, trying to solve the above problem, would have an

incentive to look for new bacterial species and strains, to solve the above problem. In particular the data of D4 and D5 provides a clear incentive to look for new isolates among the species known to be involved in periodontal diseases such as Tannerella forsythensis (which is the new designation for Bacteroides forsythus, see for example D2) and/or new species among the genera known to be involved in periodontal diseases such as Porphyromonas. Thus the present contribution, merely the provision of isolates/species of Bacteroides denticanoris, Porphyromonas levii and Tannerella forsythensis, is a selection among the hundreds of bacterial isolates/strains involved in periodontal diseases in companion animals. In order to be inventive, such a selection must not be arbitrary, but must be justified by the technical purpose, i.e. by a hitherto unknown or unexpected technical effect, caused by those technical features which distinguish the claimed bacterial isolates involved in periodontal diseases from numerous other ones. Due to the absence of any unexpected function or technical effect of the claimed bacterial isolates, the present selection amounts to nothing more than an arbitrary selection. Consequently, the subject-matter of **claims 1-35**, which is directed to or referred to said bacterium or bacteria culture does not meet the requirements of Article 56 EPC.

2.4 Statement with regard to industrial applicability (Article 33 (4) PCT)

For the assessment of the present **claim 18** on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Additional remarks concerning support of the claimed matter (Articles 5 and 6 PCT)

A) Overall lack of clarity

The claims on file refer to a percent homology. However, homology is not clear in the sense of Article 6 PCT, because it is vague and indefinite (PCT Guidelines, 11.03.2004, Chapter 5.34), and, in contrast with the term "identity", cannot be quantified: a molecule is or not homologous to another molecule. The appropriate terminology is to refer to a percent of identity, as stated in the specification on page

9, lines 5-6.

B) Claim 19

B1) The subject-matter of **claim 19** is not clear in the sense of Article 6 PCT, because it is defined by the result to be achieved. Such a definition is generally not allowable, as clearly stated in the PCT Guidelines, 11.03.2004, Chapter 5.35, because it merely amounts to a statement of the underlying problem. Such a definition is only allowable if (1) there is no other information available in the application which could have enabled the applicant to define the product satisfactorily by reference to its composition, structure or some other parameters and (2) if the result can be directly and successfully checked, by the use of test and procedures clearly specified in the description and requiring nothing more than simple test. This is not the case in the present application, since one technical option, the 16S RNA DNA sequence, is disclosed within the dependent claims and the description.

B2) Moreover, the application has provided technical support for only a very limited number of ways of measuring the presence of the indicated bacteria - by measuring the presence of the corresponding 16S RNA DNA sequence - whereas the claims embrace all possible technical options of arriving at the desideratum Consequently, the ISA considers that claim 19 does not meet the requirements of **Articles 5 and 6 PCT**, because it is insufficient to enable the skilled person to carry out the invention over the whole of the broad field claimed, without undue burden and without inventive skills.